Gender-Related Differences in Ventricular Repolarization: Beyond Gonadal Steroids

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Editorial Comment

Gender gap in cardiac repolarization has been a "puzzle" to investigators.[1] There is no difference in QT interval during childhood between boys and girls.[2] After puberty, women show longer corrected QT (QTc) interval than men due to significant shortening of QTc interval in men during the puberty.[2,3] The analysis of QT interval over various heart rates by Lehmann[4] showed that the sensitivity of QT interval to changes in heart rate is less pronounced in men than women and this was more significant at slower heart rates (i.e., 40 beats/min). They observed this phenomenon in both normal subjects and patients with long QT syndrome (LQTS). Bidoggia et al. showed that virilized women have shorter QTc interval than normal women and castrated men.[5] Rodriguez et al. demonstrated that there is an inverse correlation between progesterone level (and not estrogen) and mean QTc interval in ibutilide-treated women, and hence the risk of drug-induced torsades de pointes (TdP) was lower during luteal phase of menstruation.[6] In accordance with their findings, Rashba et al. showed that the postpartum period with a sudden drop in progesterone level is associated with a significant increase in the risk of cardiac events in LQTS.[7] Further studies are warranted to clarify the potential role of progesterone in modulation of cardiac repolarization.

Although MacFarlane et al. showed no gender difference in QT dispersion,[8] Makagawa and his colleagues showed that the *transmural* dispersion of repolarization is smaller in women than men.[9] This may help to explain why at any level of multivariate risk and even after adjusting for the difference in coronary artery disease, women are less vulnerable to sudden cardiac death than men, despite having longer QTc interval.[10] In addition, the larger spatial dispersion of repolarization in men could explain the higher event rate in LQT3 men than women.[11]

In addition to differences in the above-mentioned indices, women are more susceptible to development of TdP during various setting and constitute two-third of cases of drug induced TdP.[2] The risk of drug induced TdP does not change after menopause,[12] arguing against the role of estrogen.

The international LQTS registry was started in 1979 and has provided further evidence on gender differences in clinical course of various subtypes of LQTS.[13-16] The earlier reports of this registry[13,14] showed that in males, the risk of cardiac events (syncope, nonfatal cardiac arrest, and sudden cardiac death) was higher in childhood and decreased after puberty; in females, the risk of cardiac events did not decrease in adulthood. However, the recent reports from this registry suggested that in LQTS carriers with age $\leq$15 years, there was a significantly lower risk of cardiac events in LQT1 females than in LQT1 males. However, at variance with earlier observations,[13] in LQT2 and LQT3 children there was no difference between male and female carriers. Among LQTS carriers aged 16–40 years, the risk of first cardiac event was higher in female carriers of LQT1 and LQT2, but not LQT3.[15]

Priori et al. have recently shown that among 647 patients with various LQTS mutations, genetic locus and QTc, but *not* sex, were independent predictors of first cardiac event before age of 40 years. However, the role of sex varied according to genetic locus. Among patients with LQT2, the probability of becoming symptomatic among female patients with QTc $<$500 ms was four times as high as men with same QTc intervals, but the magnitude of this effect was less prominent among those with QT $>$500 ms.[16] However, the *lethality* of the events in LQT1 and LQT2 men was higher, probably due to slower heart rate in adult males, which could increase non-self-terminating episodes of TdP.[15]

Several investigators have suggested that gender can influence the response to therapy with β-adrenoreceptor blockers. Among 87 genotyped LQTS patients, treatment with β-adrenoreceptor blocker results in greatest shortening of the QTc interval in adult male carriers of LQT1 than females.[17]

Experimental Evidence

The bulk of evidence has revealed gender differences in ventricular repolarization in adult rabbits,[18-23] mice,[24-27] and other species.[28,29] Although it has been shown that estrogen reduces I_{CaL}, alters the dispersion of I_{CaL} across the ventricular wall, inhibits the I_{ks} and I_{kr}, and its deficiency increases the expression of I_{CaL}, testosterone has been implicated as the major factor contributing to shorter QTc interval and lower risk of TdP in a variety of adult male animal models compared to female ones. Several experimental studies showed that testosterone increases I_{kr} and I_{kur}, and hence shortens QT interval and modulates the arrhythmogenic substrate in various species, and androgen deficiency, by decreasing I_{kr} and I_{kur} can prolong action potential duration, QTc interval, and increase the risk of TdP.[18-29]

In this issue of the *Journal*, Liu et al. reported some fascinating observations regarding gender-related differences in ventricular repolarization and arrhythmia susceptibility in prepubertal rabbit heart with E4031-induced LQT2.[30] They showed that in prepubertal rabbit hearts mean action potential

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duration was longer in females than males. However, in response to an I_{kr} blocker (E4031), the prolongation of action potential duration was "considerably" more pronounced in male than female prepubertal rabbits. In addition, E4031 altered the repolarization direction.[30] The authors clearly showed that the underlying mechanism(s) of gender difference in cardiac repolarization does not confine to effects of gonadal steroids. Idriss et al. have recently studied the age-dependent changes of repolarization in rabbits and showed that the transmural dispersion of repolarization was age dependent and "developmentally determined."[31] As sex hormones could not be implicated in the above-mentioned findings, it could be assumed that in addition to gonadal steroids, other age- *and* sex-dependent developmental factors contribute to the observed difference in prepubertal rabbits. Hence, sex modulation of other ionic currents like I_{CaL}, I_{to}, and Na/Ca exchanger might be implicated in this process. Further studies are warranted to clarify the underlying mechanisms of the gender-based differences in normal state and prepubertal models of various subtypes of LQTS.

Several points in this study merit consideration. The more pronounced prolongation of APD in male prepubertal rabbits in response to E4031 might be due to greater I_{kr} current compared to females. So, the sex-hormone-independent modulation of K^+ currents by autocrine action of rennin–angiotensin and endothelin systems,[32] or other yet unidentified genetically determined factors could be implicated in this process. QTc interval is a major determinant of arrhythmogenesis in experimental models and clinical subtypes of LQTS. Therefore, the greater incidence of arrhythmia induction in prepubertal male rabbits treated with E4031 is somehow expected; however, other factors like difference in transmural dispersion of repolarization could also be implicated in the observed increased prevalence of TdP, which warrants further studies.[11]

The interesting work of Liu and his colleagues has provided us with more "known" *and* "unknown" pieces of gender repolarization gap "puzzle"[1] and has presented a novel model for studying and finding the possible sex-dependent "non-hormonal" modulating factors that underlie the gender-based differences in ventricular repolarization in normal and abnormal settings. Finding these modulators of cardiac repolarization could pave the way for better understanding the arrhythmogenesis and finding novel approaches to antiarrhythmic therapy in LQTS, and possibly other arrhythmogenic conditions.

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